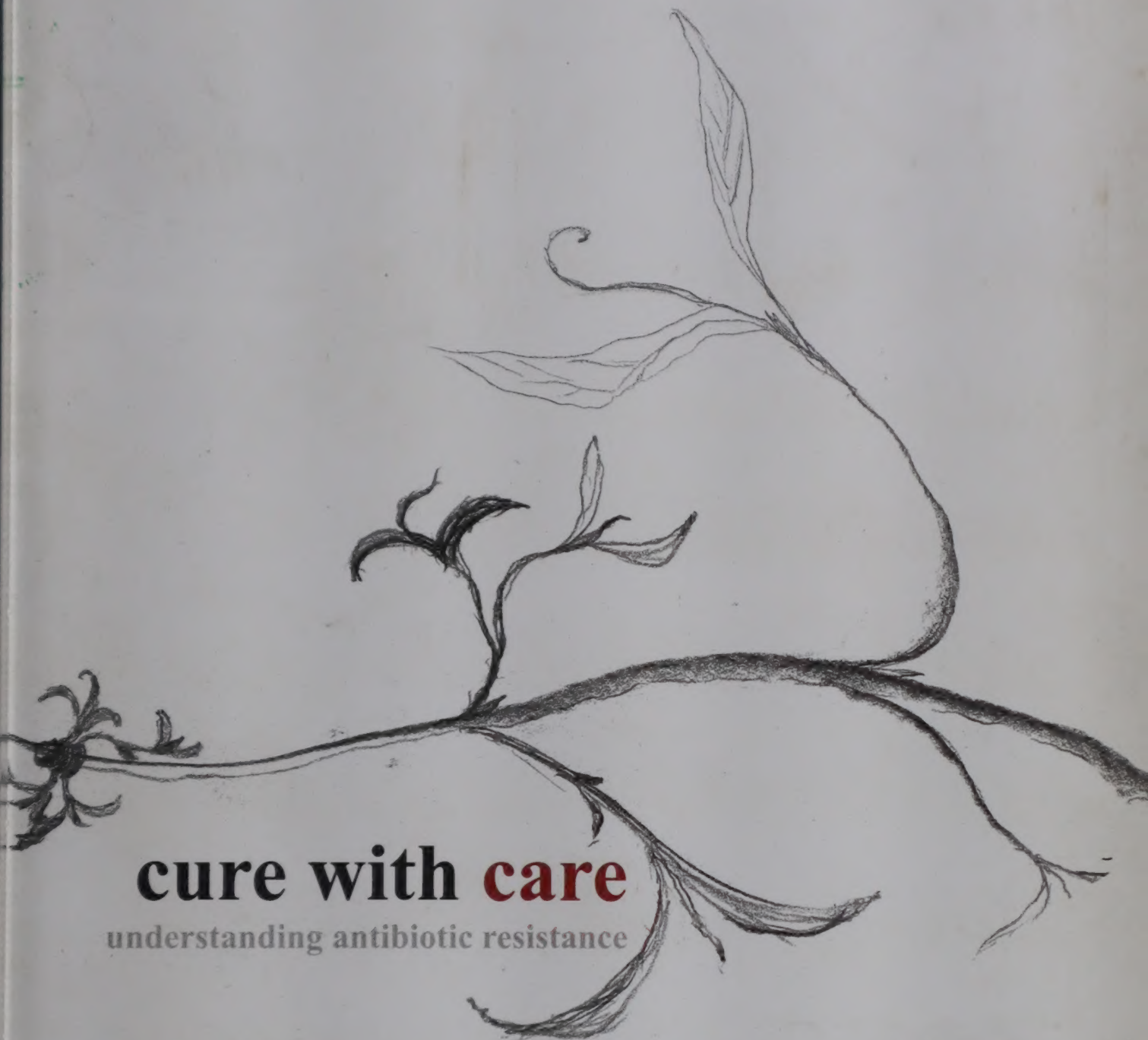

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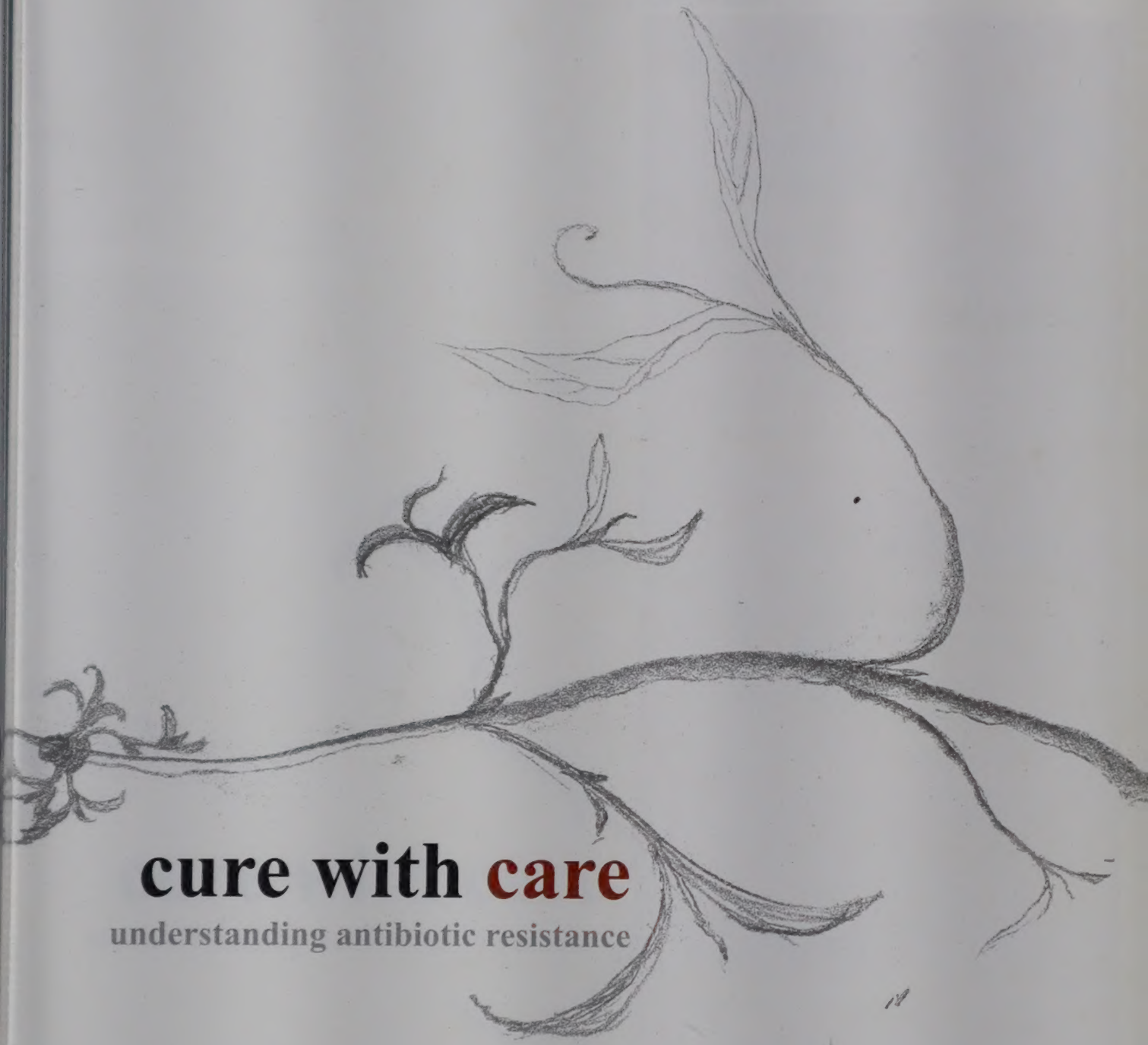

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understanding antibiotic resistance

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Introduction

It is a catastrophe that our planet faces due to the long-term impact of human activity on the natural world.

The impact is already being felt in some ways but the real damage still lies ahead of us, at the most a few decades away.

And it is a problem that can be tackled if collective action is taken by all those concerned to bring about significant policy and behavioural changes now.

Surely we are talking of global warming, the 'hottest' theme on everyone's minds these days? No, in fact we are referring to another and equally significant threat that confronts our world - that of antibiotic resistance - the phenomenon of pathogenic bacteria becoming immune to antibiotic medication.

While global warming is all about the damage wrought by human intervention to macro-ecosystems antibiotic resistance is the story of what we have done to micro-ecosystems- in particular the universe of microbes, the oldest form of life on Earth. In the frightening way our planet seems to be developing resistance to the presence and activities of human beings living on it similarly the invisible world of bacteria and viruses too have become resistant to our attempts to control and tame them.

In other words, while global warming threatens to bring the skies crashing upon our

heads antibiotic resistance, silent and faceless, is crumbling the ground beneath our feet.

Of course this is not a new problem sprung upon us suddenly by the vagaries of Mother Nature.

The resistance of bacteria to antibiotics was evident within just a few years of the introduction of these miracle drugs over six decades ago and in the past thirty years this has also been the focus of much concern among medical professionals, public health specialists and even consumer groups.

In other words, while global warming threatens to bring the skies crashing upon our heads antibiotic resistance, silent and faceless, is crumbling the ground beneath our feet

Over the years of course there has been some success in changing policies, ensuring best practices and changing behaviour of both medical practitioners and patients towards the abuse and misuse of antibiotics. However despite committed work by dozens of groups, individuals and institutions the change has not been commensurate with the sheer scope of the threat involved.

There are several reasons for the apparent complacency among policy makers, in many parts of the world, when it comes to the problem of antibiotic resistance.

Herald Tribune

Death of 4 Children Amplifies Threat From Drug-Resistant Bacteria

By Sheryl Gay Stolberg

WASHINGTON — More than 200 people in Minnesota and North Dakota have become sick, and four children dead, over the past two years after becoming infected with a drug-resistant germ that until recently has been confined to hospitals and nursing homes, federal health officials said Thursday.

The fatalities are the first to be reported in the United States, and are worrisome because they suggest that a lethal strain of Staphylococcus aureus may threaten the public. Some cases were reported last year among youngsters in Chicago and Tennessee.

The children ranged in age from 1 to 13 and had various symptoms, including extremely high fever, rash, low blood pressure and difficulty in breathing.

All were treated in the hospital with very powerful antibiotics that, should have worked against the strains. But they

Information Deficit

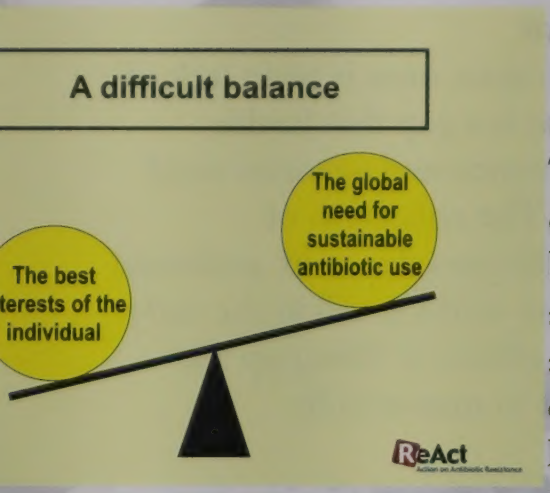
One of the most obvious ones is plain lack of information and that is a gap that health activist groups and concerned agencies need to address urgently. The collection of systematic data on the prevalence of antibiotic resistance around the world is still in the early stages and ongoing efforts at filling up the evidence gap are yet to mature fully.

Compounding this situation is also the fact that public funding for research on antibiotic resistance has been low. In most industrialised countries the problem has been considered an annoying but inevitable side effect of antibiotic use, and the epidemiological and societal aspects of antibiotic resistance have been neglected while the research agenda has been decided by the pharmaceutical industry.

Communication Gap

Secondly, to describe the public health consequences of antibiotic resistance is difficult and challenging because the problem of resistance involves diverse pathogens, transmitted in unique ways, which cause a wide range of diseases.

The consequences for the patient, such as a prolonged disease or increased mortality, which could be attributable to antibiotic resistance, are hidden within a variety of clinical syndromes and the present difficulties of measuring this resistance. Since antibiotic resistance is not of itself a disease entity, invisibility characterises the issue, making it unknown and faceless for many people



outside the medical field.

Complacency Factor

Thirdly, because of the previously continuous development of new antibacterial agents it has been possible, in countries where new drugs are affordable, to change the therapy to new antibiotics when resistance levels to older ones have become 'uncomfortably' high. This has not been possible in poor countries where many of the second and third line therapies for drug-resistant infections are unavailable, making the potential harm of resistance to first line antibiotics considerably greater.

The situation is now changing in industrialised countries, too. Because of the virtually empty pipeline of new drugs, clinicians are now facing a situation where the likelihood of success from empiric antibiotic treatment is reduced and where patients are sometimes infected with bacteria resistant to all available antibiotics.

The Numbers Game

Yet another reason for the low priority accorded by policy makers to antibiotic resistance issues is that despite the steadily increasing human toll extracted by untreatable bacteria, the numbers are still not as visible as for other pressing public health problems such as AIDS, infectious diseases such as malaria and tuberculosis or even the annual carnage wrought by traffic accidents globally. However, the key point to note about the problem of antibiotic resistance is that the potential danger it poses to the world cannot

be evaluated on purely quantitative grounds alone and one has to take a close look at the quality of threat involved.

Given how critical use of antibiotics is to an entire range of medical procedures from cardiac surgery to organ transplantation their loss of efficacy due to resistance is likely to collapse some of most significant achievements of all modern medicine.

Without efforts to check and roll back the problem of resistance our world could also go back to the pre-antibiotic era, where

Without efforts to check and roll back the problem of resistance our world could also go back to the pre-antibiotic era, where thousands died routinely due to simple bacterial infections

thousands died routinely due to simple bacterial infections. All those in any position of responsibility anywhere should do all they can to avert this dire possibility.

It is precisely for this reason that we at ReAct -Action on Antibiotic Resistance - have come together to find ways of tackling the problem in all its dimensions in a holistic manner eschewing a purely bio-medical or technical approach.

We owe it to the future of our children to preserve the enormous medical benefits antibiotics have brought to humankind.

Antibiotic Resistance - An Overview

A Clear And Present Danger

A potential post-antibiotic era is threatening present and future medical advances. The current worldwide increase in resistant bacteria and, simultaneously, the downward trend in the development of new antibiotics have serious implications.

Resistant bacteria dramatically reduce the possibilities of treating infectious diseases effectively and multiply the risks of complications and a fatal outcome for patients with infections of the blood.

Most vulnerable are those with weakened immune defences, such as cancer patients, malnourished children and people who are HIV-positive, for whom adequate therapy to prevent and treat severe infections is often necessary for their survival. In addition, antibiotic resistance jeopardizes advanced medical procedures such as organ transplantations and implants of prostheses, where antibiotics are crucial for patient safety and to avoid complications.

Mortality as a result of infectious diseases represents one-fifth of global deaths[1]; respiratory infections are the leading killer, causing nearly four million deaths annually. These deaths are to some extent regarded as preventable with increased access to health

care and medicines. However, the global emergence and spread of bacteria that resist antibiotics is raising the question as to whether this is still the case, especially in parts of the world where second and third line antibiotics are unavailable.

The Global Dimension

No country today on its own can isolate itself from resistant bacteria. Antibiotic resistance is a growing international problem affecting both current and future generations. Resistance that develops in one area of a country may easily spread nationwide.

Globalisation, with increased migration, trade and travel, has widened the range for infectious diseases. A resistant strain of *Streptococcus pneumoniae*, first identified in Spain, was soon afterwards found in Argentina, Brazil, Chile, Taiwan, Malaysia, the USA, Mexico, the Philippines, the Republic of Korea, South Africa and Uruguay[2].

Such examples underline the fact that no single country can protect itself from the threat of resistant bacteria as pathogens are spreading across international, cultural and ethnic boundaries. Although the effects of antibiotic resistance are more documented in industrialised countries, there is a greater potential for harm in the developing world.

The History

In the late 1940s, after less than a decade of penicillin being used to treat patients with infectious diseases, unresponsive strains of the bacterium *Staphylococcus aureus*, the leading

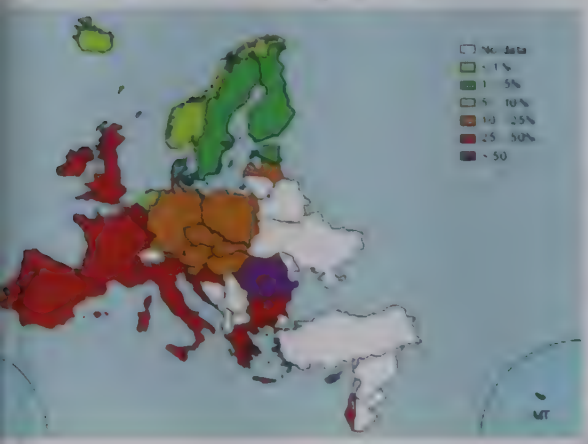
cause of hospital-acquired infections, were detected in English hospitals[3]. A striking example of biological evolution had begun: bacterial strains with natural and acquired resistance were being selected as a result of the use of antibiotics.

About a decade later the first report on resistance to the second generation of penicillin arrived; it came from a Boston hospital, where Methicillin-Resistant strains of *Staphylococcus aureus* (MRSA) had been identified.[4] MRSA has become a symbol of antibiotic-resistant bacteria and is without doubt one of the best-studied pathogens. Since the 1980s the frequency of isolates of MRSA among *Staphylococcus aureus* has increased from close to zero to nearly 70 per cent in Japan and the Republic of Korea, 30 per cent in Belgium and around 40 per cent in the United Kingdom and the United States.

It was discovered that mechanisms of resistance could be spread horizontally between different strains and different bacteria and that, consequently, clones with multi-resistant qualities could develop. The problem soon became serious for other pathogens as well. Infections caused by multi-resistant bacterial strains such as *Acinetobacter* and *Stenotrophomonas* can in some cases no longer be treated with modern antibiotics and the only available treatment is an old antibiotic, colistin, earlier rejected for clinical purposes due to its toxic side effects.

Globally, escalating levels of the multiresistant

MRSA in Europe 2005



Staphylococcus aureus: Proportion of invasive isolates resistant to oxacillin (MRSA) in 2005. Source: http://www.earss.rivm.nl

Note: True population-based estimates of the prevalence and incidence of healthcare- and community-acquired MRSA are lacking for many countries

intestinal pathogens *Salmonella* and *Shigella* cause severe infections that are difficult to treat, especially in children. In *Shigella* strains from Indonesia, Thailand and India 80- 90 per cent resistance is seen for two or more antibiotics.[5] Resistance to remaining effective therapy, such as fluoroquinolones, is steadily increasing, and the industry pipeline for antibiotics against important intestinal pathogens is running dry.

Reasons For Resistance

Resistance is a natural biological outcome of antibiotic use. The more we use these drugs, the more we increase the speed of emergence and selection of resistant bacteria. In human use, a significant majority of antibiotic consumption takes place in the community; a large part is considered based on incorrect indications, mostly viral infections.

It is estimated that over 50 per cent of antibiotics worldwide is purchased privately, from pharmacies or in the informal sector from street vendors, without prescriptions

The mechanisms behind this overuse are many and intricate. The short-term advantages of antibiotic use for patients, health care workers and drug distributors seem to overweigh concerns about future consequences.

The almost overwhelming complexity of factors influencing antibiotic consumption includes cultural conceptions, patient demands, diagnostic uncertainty, economic

incentives, the level of training among health staff and pharmacists, and advertising to prescribers, consumers and providers from the pharmaceutical industry.

In Europe, antibiotic consumption is four times higher in France than in the Netherlands[6] although the burden of disease is very similar in the two countries. Studies from some developing countries show that several antibiotics are generally prescribed at each consultation.[7]

The relationship between antibiotic use and resistance is complex. Underuse, through lack of access to antibiotics, inadequate dosing and

In Europe, antibiotic consumption is four times higher in France than in the Netherlands although the burden of disease is very similar in the two countries

poor adherence to therapy, may play as important a role in driving resistance as overuse.[8] The use of broad-spectrum antibiotic agents as a substitute for precise diagnostics or to enhance the likelihood of therapeutic success increases the rate of selection of resistant bacteria.

In addition, counterfeit and substandard drugs contribute to sub-optimal concentrations of antibiotics, failing to control bacterial populations that are considered a risk factor for developing resistance. It is estimated that over 50 per cent of antibiotics worldwide is purchased privately, from pharmacies or in the informal sector from street vendors, without

prescriptions. Half of the purchases are for one-day treatments or less, an example reflecting the magnitude of the problem.[9]

Once resistant strains are selected, their spread is promoted by factors such as overcrowding and poor hygiene together with high antibiotic use. One example is day care centers, which provide ample opportunities for the transmission of infectious diseases and, in particular, the emergence of resistant *Streptococcus pneumoniae*. The combination of the presence of young, susceptible children suffering from recurrent infections and the use of multiple, often broad-spectrum antibiotics makes such environments ideal for the carriage and transmission of these bacteria.

In the hospital setting, some bacterial clones have been more successful than others in spreading extensively. One example of the rapid dissemination of such epidemic clones is the MRSA epidemic in England and Wales where the frequency of MRSA among *Staphylococcus aureus* in blood cultures increased from less than 5 per cent in 1994 to present levels of just below 50 per cent.[10]

Antibiotics For Non-Human Use

Following their success in medicines for human beings, antibiotics have been increasingly used to treat and prevent diseases in animals, fish and plants. Besides this, sub-therapeutic doses of antibiotics have been shown to have growth enhancing effects and have for decades been intensively used in animal-rearing practices. In Europe

and North America, antibiotic use in the animal sector constitutes around half of the total consumption.[11]

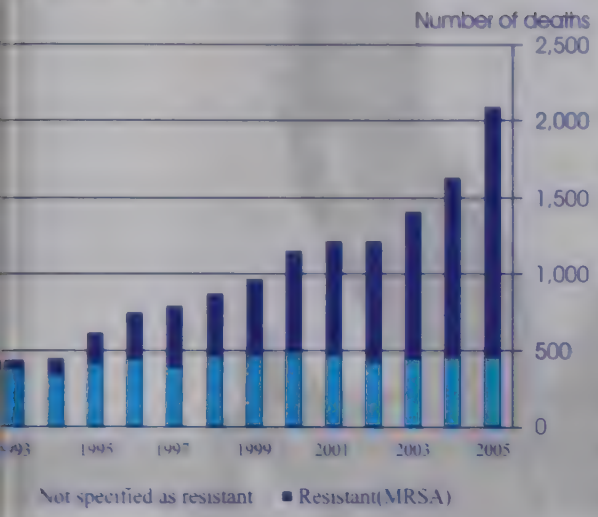
In 1987 more than 90 per cent of the drugs used on animals in the United States was administered without veterinary consultation.[12] Within the European Union most antibiotics in feedstuff have been prohibited for a number of years, but in many countries large numbers of animals, irrespective of their health status, are exposed daily to sub-therapeutic concentrations of antibiotics. Some growth promoters belong to groups of antibiotics, such as glycopeptides, that are essential drugs in human medicine for the treatment of serious, potentially life-threatening infections. Emerging multiresistant bacteria from farm animals are transmitted to humans mainly through the food chain or by direct contact. The parallel emergence in animals of resistant strains, especially of *Salmonella* and *Campylobacter*, is continuously bringing in new clones that cause infections in human beings.

Mortality, Costs And Ecology

Through the selection pressure caused by antibiotic use, a large pool of resistant genes has been created. Today, we are starting to see the tip of the iceberg. Slowly, the health impact is emerging.

Failure of the initial antibiotic regimen due to resistant bacteria increases the risks of secondary complications and a fatal outcome, underscoring the clinical dilemma of empirical

Number of death certificates with MSSA/MRSA as underlying cause, UK[13]



therapy and the prevailing lack of rapid diagnostic tests.

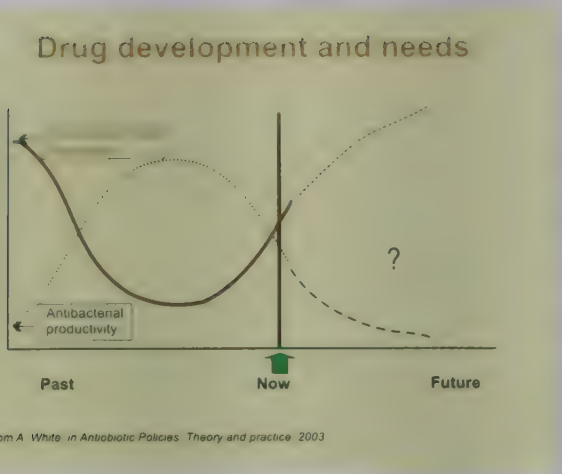
Recently, a study in intensive care demonstrated significantly higher mortality among patients that received inadequate empirical therapy, compared with those given adequate therapy (42 vs. 17 per cent).[14] Consequently, there is a clear justification for initial broadspectrum therapy in severe infections. This moves us into a vicious circle where increasing levels of resistance necessitate the use of broader, more potent antibiotics to secure patient survival but where using these reserve antibiotics escalates the problem as resistance develops and creates a situation where effective antibiotics are lacking.[15]

System Failure

Soon after the introduction of penicillin a thorough inventory of biological compounds with antibiotic activity was undertaken. Substances with different target mechanisms to attack bacteria were developed into new categories of antibiotics by the pharmaceutical industry and were eagerly used by medical professionals in their clinical practice. For many years, society's medical needs for antibacterial drugs were met by the pharmaceutical industry.

In 1987 more than 90 per cent of the drugs used on animals in the United States was administered without veterinary consultation

An apparent symbiosis between the interests

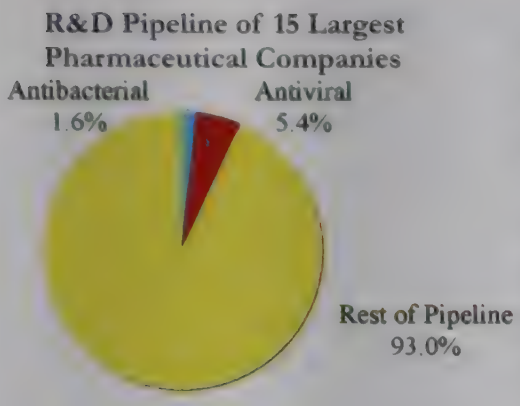


of the community and those of the industry prevailed. In the 1970s, innovative research to develop new antibiotics gradually waned, and the focus of research and development shifted to the fine-tuning of existing products. As resistance to antibiotics accelerated, the fragile relationship between the community and the pharmaceutical industry began to break down.

New antibiotics almost instantly faced the problem of the evolution of bacterial resistance after being put on the market and the short durability of antibacterial drugs was giving pharmaceutical companies cold feet. The industry began increasingly to weigh up its liabilities towards shareholders on the one hand and public trust and accountability to the community at large on the other. Difficulties arose as financial performance confronted the common good.

From a broad societal perspective, the industry might be expected to supply communities with good drugs at affordable prices and provide reliable information on them. Today, this is not the case.

The cleft between public and private interests grew wider with the development of national and international drug policies aimed at containing resistance and restricting and rationalizing the use of antibiotics. Sharpened demands from regulatory bodies have increased the development cost of new medicines, and prioritising measures to secure



Source: Data from Spellberg (2004)

optimal returns on investment have driven the industry into other pharmaceutical areas with bigger and safer markets.

At present, the industry's ventures are shifting from therapy for acute conditions towards long-term treatment of chronic diseases. Prospective investments in antibiotics are more than ever competing with drugs for musculo-skeletal and neurological diseases with 10 or 15 times greater 'net present value', a measure used by the industry to predict the potential success of products.

However, the need for antibiotics is anticipated to remain consistently high. From a broad societal perspective, the industry might be expected to supply communities with good drugs at affordable prices and provide reliable information on them. Today, this is not the case.

It is clearly time for radical change.

What Needs To Be Done?

Although the full magnitude of the consequences of antibiotic resistance for society is still unclear, awaiting more data before taking further action to contain their spread is not an appealing option. Continued complacency is unjustifiable and even unethical in contexts where the lack of effective antibiotics is most imminent.

Rational Use of Drugs

An important reason for antibiotics losing their effectiveness is due to their widespread irrational use through wrong selection or taken in courses cut short by the expense of these drugs.

Thus, rational use of medicines is essential to responding to this public health challenge. Health care providers, pharmacists, consumers, and communities all over the world need to be supported to be more independent and knowledgeable about prescribing, recommending or matching medicines to people's needs.

Raising Awareness

Social constraints and cultural views of infectious conditions that require antimicrobial treatment exert a strong influence on their use, particularly for community-acquired pathogens.

Several countries have recently taken the bold step of launching national campaigns to educate physicians and patients about antimicrobial misuse and the threat of

resistance. These campaigns show promise in changing attitudes and behavior, among both the public and healthcare professionals . If repeated regularly, the campaigns are likely to reduce inappropriate patient requests for antimicrobial agents, which in conjunction with physician education models may reduce inappropriate antimicrobial prescription practices

Better Diagnostics

Diagnostic uncertainty is a key driver of drug misuse and overuse, which can lead to antimicrobial selection pressure and increased rates of resistant microbes . The risks associated with untreated microbial infection and the lack of accurate clinical or

Continued complacency is unjustifiable and even unethical in contexts where the lack of effective antibiotics is most imminent

laboratory prediction methods result in a low threshold for initiating empirical antimicrobial drug therapy, especially if infection could be life threatening.

The availability of rapid diagnostics would help rational use and prolong the lifespan of available drugs.

New Drugs

Only two new classes of antibiotics have been brought to the market in the past 30 years. It is already clear that new treatments are needed for hospital-acquired Gram-negative bacterial infections, for community-acquired resistant

infections, and for infections common in developing countries such as tuberculosis and typhoid fever.

Vaccinology
The development of new vaccines is likely to contribute to the decreased transmission and impact of antimicrobial-resistant bacteria. More so than antimicrobial agents, vaccines have the potential to durably control infectious agents by blocking their ability to disseminate within a population.

Fresh Investment in R&D
To attract the industry sufficiently to return to investing in new antibiotics may require

The availability of rapid diagnostics would help rational use and prolong the lifespan of available drugs

concrete measures, including reducing the costs of research and development as well as securing the longer use of products.

These ideas are not new. In the area of neglected diseases an 'orphan drug system' has developed to stimulate production of necessary drugs. Extended patents have also been discussed as a way of directing industry investments. Increasing the returns on investment is the obvious key factor in promoting drug development within the existing framework; but can alternative options be found outside the existing structures? Using a public health approach to fill preventive and curative gaps in respect of

diseases where the industry has lost interest would be an attractive path to explore.

The prevailing perplexity of governments in the face of the need to balance commercial and community interests in this issue must be resolved. At present, public and private interests are at odds society's continuously high needs contrasting with the diminished accountability of the pharmaceutical industry. Incentives for the development of new antibacterial drugs with novel mechanisms of action are essential.

Healthcare Regulation

Antimicrobial use is affected by reimbursement policies, financial incentives, and healthcare regulation. There are several examples of how regulation can positively influence rational use of antibiotics.

Since 1999, the Chilean Ministry of Health has strictly enforced existing laws, which restricted purchase of antimicrobial agents without a medical prescription. These regulatory measures had a sustained impact on antimicrobial use in the outpatient setting: sales of orally used antimicrobial agents decreased by 43% from US $45.8 million in 1998 to US $26.1 million in 2002.[16]

Again, in 2000, against the strong opposition of physicians and the pharmaceutical industry, a new Korean government policy prohibited physicians from dispensing drugs and pharmacists from prescribing drugs. This new policy decreased overall prescribing of

antimicrobial agents and selectively reduced inappropriate prescribing of them for patients with viral infections.[17]

Global Action Needed

International collective action is essential, yet responsibility for health remains predominantly national. Consequently, there is a potentially significant disparity between the problems and potential solutions associated with antibiotic resistance and the institutions and mechanisms available to deal with them. Comprehensive recommendations on rationalising antibiotic use, from the World Health Organization, the European Union and other multilateral organisations, get lost when it comes to translating them into action plans in individual countries.

The difficulties of enforcing these recommendations on a global level are evident. Presently, the links between the well-formulated strategies at the level of global society and their acceptance by national policy makers are weak.

To identify these barriers so as to prevent the message from repeatedly being returned to sender is a major challenge, but one that needs to be overcome urgently.

ReAct

Action on Antibiotic Resistance

Vision, Mission, Values And Strategies

ReAct, Action on Antibiotic Resistance, is an international coalition of individuals, organisations and networks committed to combating antibiotic resistance as a global threat to health.

Vision

Current and future generations will have access to effective prevention and treatment of bacterial infections as part of their right to health.

Mission

ReAct seeks profound change in the understanding of, and responses to, infection and antibiotic resistance through a social movement that engages civil society, community and consumer organisations, health policy reformers and those individuals, networks and institutions that generate and analyse health-related knowledge. ReAct will catalyse and co-ordinate action in ways most likely to make these changes.

In striving for its vision, ReAct is committed to change four fundamental dynamics underlying the ability to prevent and treat infection. ReAct believes:

- that antibiotics should be used appropriately in humans, animal and

plants their use reduced when of no benefit, and their correct and specific use increased when needed;

- that hospital and community infectious diseases should be prevented through improved infection control and better hygiene and nutrition;
- that awareness is needed of the ecological balance in all aspects of human life as part of a comprehensive and integral concept of health;
- that the root causes of antibiotic resistance, as well as effective responses, are social, political and ecological as much as scientific and technical.

Values

ReAct

- strives to base its arguments on the highest quality of science;

  maintains due respect for traditional and indigenous medical systems that may have the potential to help prevent antibiotic resistance;

- stands against the use of microbes as agents of bioterrorism and strongly opposes efforts to develop antibiotic resistant strains towards such ends;
- works towards equitable health care access for all people in its advocacy for prevention and treatment of infectious diseases;
- recognises the unequal burden of antibiotic resistance on the poor and

disadvantaged, especially women and children, and supports their advocacy for health;

- respects the right of people in all countries to informed consent, ethical standards for clinical trials, and high standards of research conduct, and requires partners joining its work to respect this principle;
- functions in a transparent manner so as to detect and avoid any conflict of interest perceived or real in its own activities to ensure the credibility of its policy voice.

Strategies

- ReAct will mobilise attention to, resources for and collaboration to combat development and spread of antibiotic resistance around the world by:
- stimulating, organising and supporting political, professional and community action;
- making the burden of antibiotic resistance more transparent to policy makers and the public, and advocating that governments set up effective systems to reduce it;
- encouraging and supporting processes of consumer and health care worker empowerment;
- building alliances with groups across various sectors, and linking to campaigns with related and shared goals, such as those dealing at global and country level

with HIV and AIDS, tuberculosis, malaria, patient safety and the rational use of medicines;

- promoting strategies for the development of new antibacterials and complementary technologies, including diagnostics and vaccines, that might reduce reliance on antibiotics;
- promoting new ways of approaching the problem of antibiotic resistance including a new understanding of the fundamental relationships, both beneficial and harmful, between humans, microbes, other living beings, infection, medicines and lifestyle.

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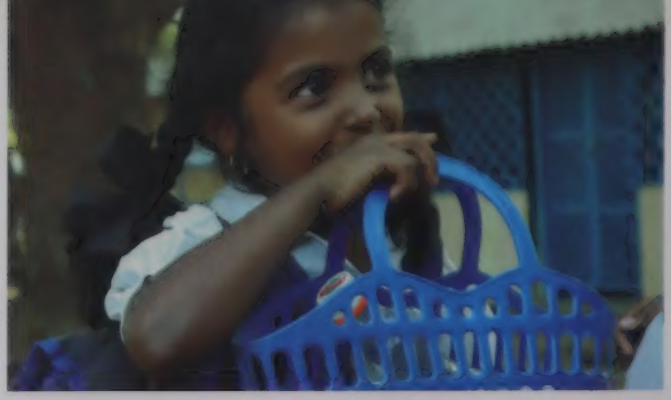
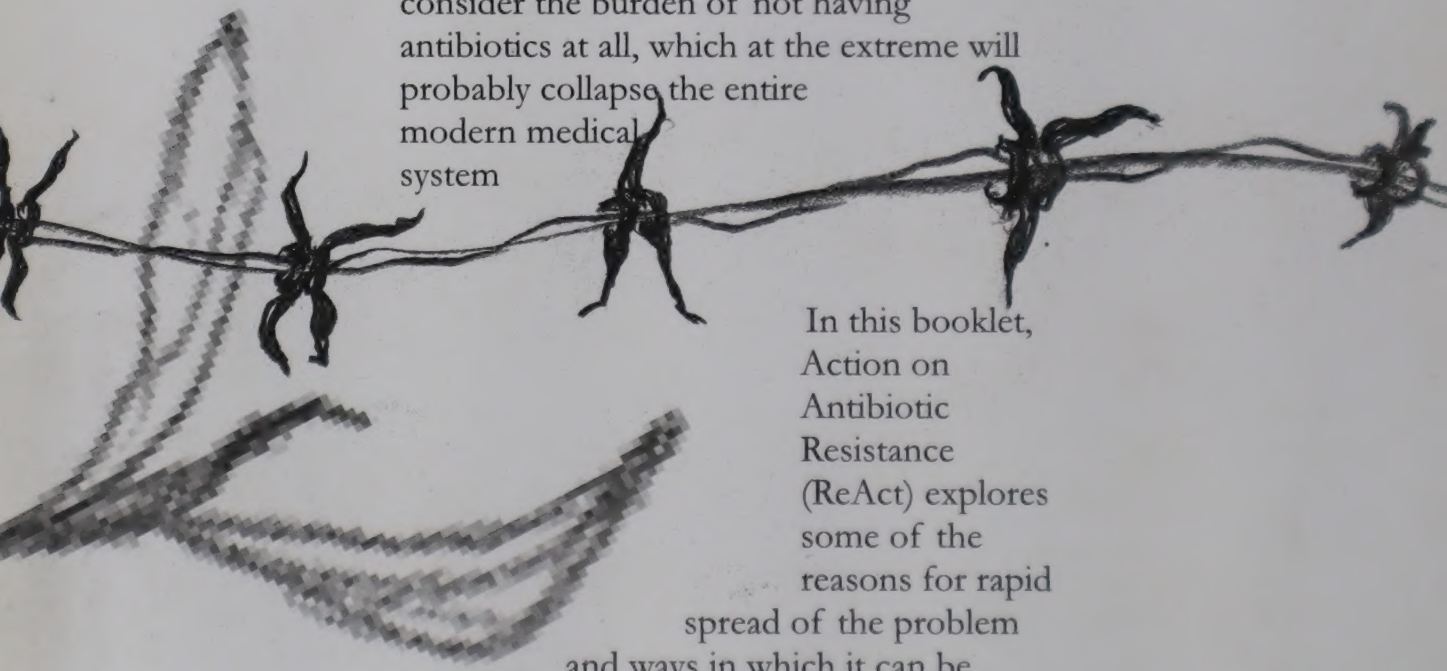


Among several alarming global public health problems with the potential to rapidly reach disastrous levels, resistance to antibiotics seems to be one of the most serious.

Antibiotics are the cornerstone of modern medicine which have revolutionized medical care in the past half a century - from cradle to grave the role of antibiotics in safeguarding the overall health of human societies is pivotal.

In order to calculate the full economic burden of antibiotic resistance we have to consider the burden of not having antibiotics at all, which at the extreme will probably collapse the entire modern medical system



In this booklet, Action on Antibiotic Resistance (ReAct) explores some of the reasons for rapid spread of the problem and ways in which it can be tackled. The booklet is aimed at policy makers and health officials everywhere but could also be a useful introductory text on the subject for all concerned.

ReAct

Action on Antibiotic Resistance

www.reactgroup.org